Studies on the Synthesis of the Mycalamides: Stereocontrolled Synthesis of a Model *N*-Glycosylpederamide via a Stereoselective Aldol Reaction

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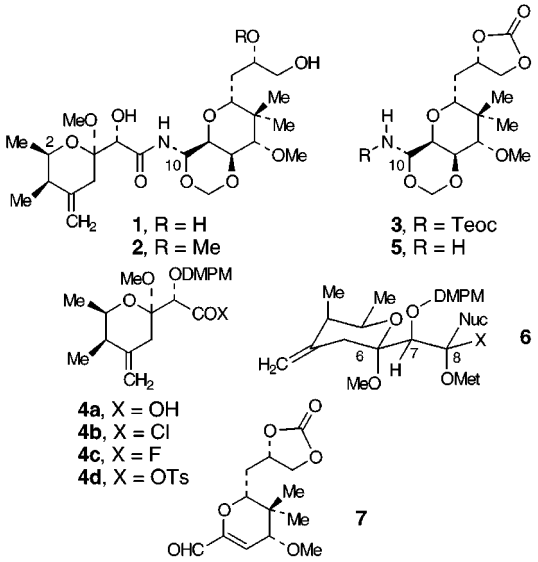
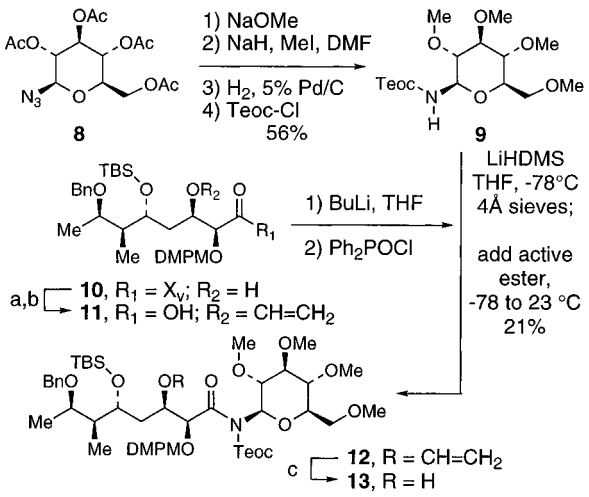
Our original plan for completion of total syntheses[2,3] of mycalamides A (**1**) and B (**2**)[4,5] called for N-acylation[6] of carbamate **3**[7] with a suitable active ester of pederic acid (see **4a**−**d**).[8] Unfortunately, repeated attempts to accomplish this key transformation by treating either the lithium or potassium anions generated from **3** (via deprotonation with *n*-BuLi, LHMDS, LHMDS−HMPA, or KHMDS in THF at −78 °C) with the acid chloride **4b** or acid fluoride **4c**[6] under a range of conditions (e.g., in the presence of added DMPU or HMPA) and reaction temperatures (−78 to 0 °C) gave none of the desired coupled product.[9] Surprisingly, both **4b** and **4c** could be recovered chromatographically from the reaction mixtures. The lack of success with this reaction can be attributed to severe nonbonded interactions that develop in tetrahedral intermediate **6**, which experiences two destabilizing gauche pentane interactions[10] no matter which rotamer about the C(6,7) or C(7,8) bonds is considered. The low reactivity of pederoyl chloride derivatives has been noted previously.[11] Attempts were also made to deprotect **3** (via treatment with TBAF in DMF) and to perform the acylation of amine **5** with the mixed anhydride **4d** according to Kishi's protocol.[2a] This, however, provided enal **7** as the major product, again with none of the desired amide being isolated.[12]



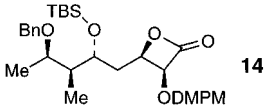
These results dictated that we examine a revised approach involving use of less advanced, less sterically congested pederic acid precursors in the carbamate acylation reaction. Because our supply of **3** was virtually exhausted, we elected to probe this strategy by using glucosylamine derivative **9** as a model system. We report herein the results of these investigations, culminating in a highly stereoselective synthesis of the *N*-glucosylpederamide derivative **22**.

Scheme 1[a]



[a] Key: (a) butyl vinyl ether, $Hg(OAc)_2$, 70%; (b) LiOH, H_2O_2, THF−H_2O, 84%; (c) OsO_4, NMO, *t*-BuOH−THF−H_2O, 69%.

Carbamate **9** was prepared from the known tetraacetyl glycosyl azide **8**,[13] while carboxylic acid **11** was prepared from the previously described pederic acid precursor **10** (Scheme 1).[8] Unfortunately, acid **11** also proved to be too hindered to undergo efficient coupling with **9**. Best results were obtained when **11** was converted to the mixed phosphinic anhydride by sequential treatment with *n*-BuLi in THF (−78 °C) followed by addition of diphenylphosphinic chloride. Addition of a solution of this active ester (1.3 equiv) to a −78 °C solution of the lithium anion generated from **9** (LiHMDS, THF, −78 °C, in the presence of 4 Å molecular sieves) with warming to ambient temperature provided **12** in 21% yield along with 63% of recovered **9**. Comparable yields of **12** were obtained with the acid chloride generated from **11**.[6] Less reproducible results were obtained when the lithium anion of **9** was treated with the mixed anhydride generated from **11** and trichlorobenzoyl chloride (10−30% of **12**; 33−42% of recovered **9**). Attempts to use β-lactone **14** as the acylating agent were unsuccessful.



(1) Correspondence to this author should be sent to the University of Michigan address.

(2) Total syntheses of mycalamides A and B: (a) Hong, C. Y.; Kishi, Y. *J. Org. Chem.* **1990**, *55*, 4242. (b) Nakata, T.; Fukui, H.; Nakagawa, T.; Matsukura, H. *Heterocycles* **1996**, *42*, 159. (c) Synthesis of 18-*O*-methyl mycalamide B: Kocienski, P.; Raubo, P.; Davis, J. K.; Boyle, F. T.; Davies, D. E.; Richter, A. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1797.

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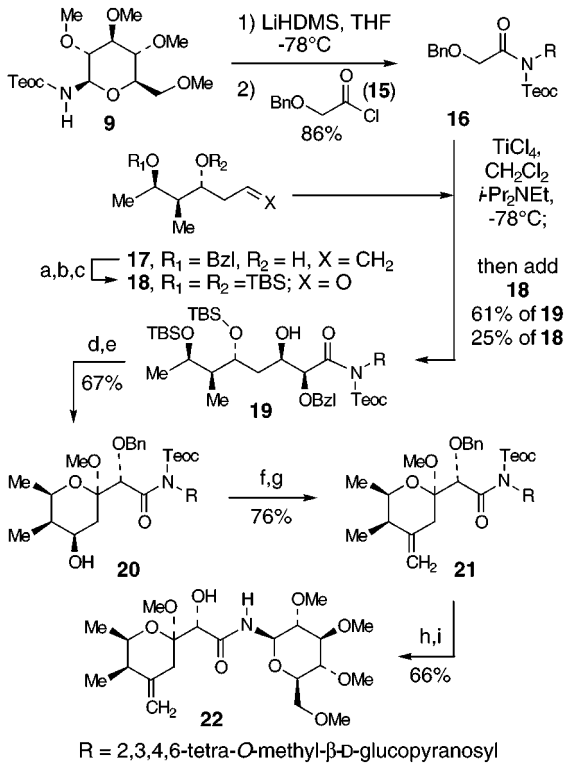
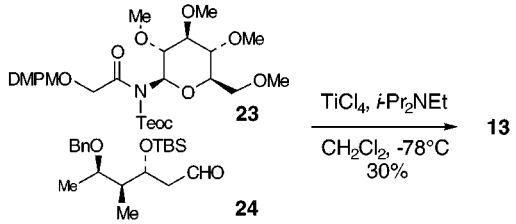
Scheme 2[a]



[a] Key: (a) Na, NH_3, −78 °C, 93%; (b) TBS−OTf, 2,6-lutidine, 92%; (c) O_3, CH_2Cl_2−MeOH, −78 °C, then Ph_3P, 86%; (d) DMSO, $(COCl)_2$, Et_3N, −78 °C; (e) CSA, MeOH, 67% for two steps; (f) DMSO, $(COCl)_2$, Et_3N, −78 °C, 88%; (g) Zn, CH_2I_2, $TiCl_4$, THF, 86%; (h) TBAF, DMF, 0 °C, 89%; (i) Na, NH_3, −78 °C, 74%.

Ultimately, a workable synthesis of the *N*-glucosyl pederamide derivative **22** was developed, involving the aldol reaction of **16** and **18** (Scheme 2). Acylation of **9** with benzyloxyacetyl chloride (**15**) provided imide **16** in 86% yield. This intermediate (3 equiv) underwent a $TiCl_4$-mediated aldol condensation[14] with aldehyde **18**, which in turn was prepared by a standard sequence of operations from **17**.[8] Interestingly, this reaction provided a single aldol diastereomer **19** in 61% yield; in addition, 25% of aldehyde **18** and 70% of **16** were recovered. The stereochemistry of **19** was assigned by analogy to **13**, which was the only diastereomer produced in the chlorotitanium aldol reaction of **23** and aldehyde **24**.[15] The stereochemistry of **13** is known unambiguously by virtue of its synthesis from **12** (vide supra). The aldol reaction of **24** and the lithium enolate of **23** was also highly stereoselective, although in this case it was not possible to suppress migration of the Teoc group from nitrogen to the resulting aldolate oxygen. No reaction occurred under standard boron aldol conditions (Bu_2BOTf, Et_3N, CH_2Cl_2, −78 to 0 °C). The excellent diastereoselectivity of these reactions appears to be due the tendency of β-alkoxy aldehydes to favor the generation of 1,3-anti products[16] and not due to a high diastereofacial bias on the part of the metal enolate,[17] since aldol reactions of **16** with achiral aldehydes provided ca. 2:1 mixtures of products.



Swern oxidation[18] of **19** gave a sensitive β-keto imide that was immediately treated with camphorsulfonic acid (CSA) in MeOH. This initiated a sequence of three functional group transformations—deprotection of the two TBS ethers and cyclization of the δ-hydroxy ketone to the methyl hemiketal unit of **20**, which was isolated in 67% yield for the two steps. Significantly, no epimerization of the C(7) stereocenter occurred under these conditions. Oxidation of **20** under Swern conditions followed by introduction of the *exo*-methylene unit by using the Takai−Nozaki protocol (CH_2I_2, $TiCl_4$, Zn, THF)[19] provided the fully protected pederamide derivative **21** in 76% yield. Finally, removal of the Teoc protecting group by treatment of **21** with *n*-Bu_4NF in DMF at 0 °C and the benzyl ether by dissolving metal reduction (Na, NH_3) completed the synthesis of the model *N*-glycosylpederamide **22**.

In summary, a highly stereoselective method for synthesis of *N*-α-alkoxy pederamide derivatives has been devised. This is only the second[3b] completely stereocontrolled synthesis of a pederamide derivative yet reported.[20] Further efforts to streamline this protocol and to utilize it to complete total syntheses of the mycalamides are in progress and will be reported in due course.

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Supporting Information Available: Experimental procedures and full characterization data for all new compounds; ^1H NMR spectra of **18**, **21**, and **22** (16 pages).

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(12) Treatment of **3** with TBAF in DMF at 0 °C followed by addition of benzoyl chloride and DMAP provided the *N*-benzoylmycalamine derivative in 34% yield as a single diastereomer. In contrast, acylation of the lithium anion of **3** with benzoyl chloride followed by TBAF removal of the Teoc unit provided the same *N*-benzoylmycalamine derivative in 87% yield (ref 7).
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